ClinicalEvidence

Appendicitis

Search date May 2014

Nigel D'Souza, Karen Nugent

ABSTRACT

INTRODUCTION: Appendicitis is an inflammation of the appendix that may lead to an abscess, ileus, peritonitis, or death if untreated. Appendicitis is the most common abdominal surgical emergency. The current standard treatment of uncomplicated appendicitis is usually surgery, but there has been increasing evidence published on the use of antibiotics. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical question: What are the effects of surgery compared with antibiotics for acute appendicitis? We searched: Medline, Embase, The Cochrane Library, and other important databases up to May 2014 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found four studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of surgery (including laparoscopic and open appendicectomy) compared with antibiotics.

QUESTIONS

INTERVENTIONS

Key points

- Appendicitis is inflammation of the appendix that may lead to an abscess, ileus, peritonitis, or death, if untreated.
- Appendicitis is the most common abdominal surgical emergency.
- The current standard treatment for uncomplicated appendicitis is usually surgical removal of the appendix (appendicectomy), but there has been increasing evidence published on the use of antibiotics.
- The evidence comparing surgery with antibiotics is weak and confounded by factors such as inconsistencies with results and outcomes measured, which makes it difficult to compare these interventions.
- Appendicectomy may be associated with reduced overall treatment failure (including recurrence requiring surgery within 1 year) in the treatment of adults with acute appendicitis, but may also be associated with an increase in complications and sick days compared with antibiotics.

  We don't know whether appendicectomy and antibiotics differ with regard to hospital stay, or in improving quality of life scores.

  We found no studies reporting outcomes beyond 1 year, which is a major limitation of the available evidence.

  All of the evidence we found was in adults; we found no RCTs in children.
- At present, the weight of evidence does not suggest that antibiotics are superior to surgery for treating appendicitis.
- There is a lack of high-quality RCTs comparing what might be termed optimal current surgical techniques with optimal current antibiotic regimens. Further trials are currently under way, which may provide further information on how current surgical techniques compare with current antibiotic regimens when both treatment approaches are optimised.

Clinical context

DEFINITION

Appendicitis is inflammation of the vermiform appendix. Progression of the inflammatory process can lead to abscess, ileus, peritonitis, or death if untreated. The term 'complicated' appendicitis refers to the presence of gangrene or perforation of the appendix. Free perforation into the peritoneal cavity can lead to purulent or faeculent peritonitis. A contained perforation can lead to appendix abscess or phlegmon (inflammatory mass).

INCIDENCE/ PREVALENCE

Appendicitis is the most common abdominal surgical emergency. The reported lifetime risk of appendicitis in the US is 8.6% in men and 6.7% in women, [1] with an annual incidence of 9.38 per 100,000. [2] In the US, it is estimated that around 326,000 operations for appendicitis were performed in 2007. [3] In the UK, around 42,000 to 47,000 operations for appendicitis were performed yearly between 2007 and 2012. [4] Large studies from the UK and US have shown that complicated appendicitis is found at surgery in around 16.5% to 24.4% of cases. [5] [6]

AETIOLOGY/ RISK FACTORS

The cause of appendicitis is uncertain, although various theories exist. The predominant theories centre on luminal obstruction of the blind-ending appendix as the primary pathology. When goblet cell secretions are blocked from escaping by the luminal obstruction, the intra-luminal pressure within the appendix increases and leads to ischaemia of the appendix wall. The translocation of bacteria from the lumen across the compromised mucosa causes transmural inflammation. Ongoing tissue ischaemia and inflammation can then lead to infarction and perforation of the appendix (complicated appendicitis). Free perforation will lead to soiling of the intra-peritoneal cavity with pus or faeces. A perforation can also be enclosed by the surrounding soft tissues (omentum, mesentery, or bowel), thus leading to the development of an inflammatory mass. This inflammatory mass may contain pus (abscess) or it may not (phlegmon). There is some debate as to whether perforated appendicitis is a disease process distinct from uncomplicated appendicitis. [7] [8] Hyperplasia of the lymphoid tissue in the mucosa or submucosa has been posited as the most common mechanism causing obstruction of the appendix lumen. This may present with acute catarrhal appendicitis, with a gradual onset of symptoms. Lymphoid hyperplasia may be caused by infections (bacterial, viral, fungal, parasitic) or by inflammation, such as in inflammatory bowel disease. Other, rarer causes of obstruction may include parasites (more common in developing countries), fibrous bands, foreign bodies, or carcinoid and caecal carcinoma. [9] A more abrupt course of symptoms has been described in acute obstructive appendicitis from faecoliths.

PROGNOSIS

The prognosis of untreated appendicitis is unknown, since RCTs comparing treatment with no treatment would be unethical. Spontaneous resolution rate of radiologically confirmed appendicitis has been reported to range from around 4% to 20%. [10] However, spontaneous resolution and recurrence of appendicitis (the 'grumbling appendix') [11] [12] remains a contentious issue among surgeons. The current standard treatment for uncomplicated appendicitis is usually surgical removal of the appendix (appendicectomy) to prevent potential complications from untreated appendicitis. There has been increasing evidence published on the use of antibiotics. [13] [14] [15] Surgical treatment is performed either through an incision (open appendicectomy) or using keyhole surgery (laparoscopic appendicectomy). One systematic review found that wound infection was less likely with laparoscopic appendicectomy compared with open appendicectomy (OR 0.43, CI 0.34 to 0.54), but intra-abdominal abscess formation was more likely with laparoscopic appendicectomy (OR 1.87, CI 1.19 to 2.93). [16] The incidences of both wound infection and abscess formation appear to be higher in complicated appendicitis. [6] A perforated appendix in childhood does not seem to have subsequent negative consequences for female fertility. [17]

AIMS OF INTERVENTION

To resolve acute symptoms (e.g., pain) with minimal adverse effects; to prevent the need for surgery (after antibiotics); to prevent postoperative complications, such as wound infection (after surgery); to shorten hospital stay; and to hasten return to normal activity.

OUTCOMES

Treatment success discharge from hospital without surgery (for antibiotics), post-treatment complications (e.g., wound infection from surgery; and perforation and peritonitis from antibiotics), treatment failure; **mortality** from appendicitis; **length of hospital stay**; **return to normal activities** (including sick leave days); **quality of life**; and **adverse effects** (including recurrence).

METHODS

Clinical Evidence search and appraisal May 2014. The following databases were used to identify studies for this systematic review: Medline 1966 to May 2014, Embase 1980 to May 2014, and The Cochrane Database of Systematic Reviews 2014, issue 4 (1966 to date of issue). Additional searches were carried out in the Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment (HTA) database. We also searched for retractions of studies included in the review. Titles and abstracts identified by the initial search, run by an information specialist, were first assessed against predefined criteria by an evidence scanner. Full texts for potentially relevant studies were then assessed against predefined criteria by an evidence analyst. Studies selected for inclusion were discussed with an expert contributor. All data relevant to the review were then extracted by an evidence analyst. Study design criteria for inclusion in this review were: published RCTs and systematic reviews of RCTs in the English language, at least single-blinded (where possible), and containing 20 or more people (10 or more in each arm) with uncomplicated acute appendicitis or appendix abscess (excluding perforated appendicitis), of whom more than 80% were followed up. There was no minimum length of follow-up. We excluded all studies described as 'open', 'open label', or not blinded unless blinding was impossible. We included RCTs and systematic reviews of RCTs where harms of an included intervention were assessed, applying the same study design criteria for inclusion as we did for benefits. All serious adverse effects or those adverse effects that are reported as statistically significant were data extracted for inclusion in the harms table of the review. Pre-specified adverse effects identified as being clinically important were reported, even if the results were not statistically significant. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA that are added to the reviews as required. To aid readability of the numerical data in our reviews,

we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as RRs and ORs. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 11). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of surgery compared with antibiotics for acute appendicitis?**

OPTION **SURGERY VERSUS ANTIBIOTICS**

- For GRADE evaluation of interventions for Appendicitis, see table, p 11 .
- The evidence comparing surgery with antibiotics is weak and confounded by factors such as inconsistencies with results and outcomes measured, which makes it difficult to compare these interventions.
- Appendicectomy may be associated with reduced overall treatment failure (including recurrence requiring surgery within 1 year) in the treatment of adults with acute appendicitis, but may also be associated with an increase in complications and sick days compared with antibiotics.
- We don't know whether appendicectomy and antibiotics differ in effectiveness at reducing length of hospital stay or in improving quality of life scores.
- We found no RCTs reporting outcomes beyond 1 year, which is a major limitation of the available evidence, and we found no evidence in children.
- In general, it was unclear from the RCTs whether people in the surgical group also received antibiotic treatment and there was no comparison of current optimal therapies.
- The specific appendicectomy technique used in the RCTs was either not reported or reported as at the surgeon's discretion (open or laparoscopic). The reviews did not perform a subgroup analysis based on the surgical techniques used.

Benefits and harms

Surgery versus antibiotics:

We found three systematic reviews (each with a search date of 2011). [13] [14] [15] The three reviews reported many of the same RCTs, but in different combinations (see Further information on studies). Each review reported a synthesis of different outcome measures and came to different conclusions; therefore, we have reported all three reviews here to cover the full spectrum of evidence.

Treatment success

Surgery compared with antibiotics Appendicectomy may be more effective than antibiotics at reducing treatment failure including recurrence at up to 1 year, but may be less effective at reducing some complications in adults with uncomplicated acute appendicitis. However, the evidence is weak and results varied by outcome measured (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Treatment success					
[15] Systematic review	Adults with acute uncomplicated appendicitis (no abscess or phlegmon) 5 RCTs in this analysis	**Initial treatment failure (antibiotic: failure to achieve definite improvement without the need for surgery and hospital discharge without an operation; appendicectomy: failure to achieve pathologically confirmed appendicitis after surgery or another surgical indication for operation)** 40/470 (9%) with appendicectomy 137/510 (27%) with antibiotics	OR 2.43 95% CI 0.94 to 6.33 P = 0.07 Significant heterogeneity: I^2 = 69%, P = 0.01 Heterogeneity not further explained	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[15] Systematic review	Adults with suspected acute uncomplicated appendicitis (no abscess or phlegmon) 5 RCTs in this analysis	**Overall treatment failure (initial treatment failure plus anyone in the antibiotic group requiring appendicectomy because of recurrence) , up to 1 year** 40/470 (9%) with appendicectomy 205/510 (40%) with antibiotics	OR 6.72 95% CI 3.48 to 12.99 P <0.00001	●●○	appendicectomy
[15] Systematic review	Adults with acute uncomplicated appendicitis (no abscess or phlegmon) 5 RCTs in this analysis	**Overall complications (e.g., surgical site infection, organ space infection, small bowel obstruction, other)** 60/510 (12%) with antibiotics 83/470 (18%) with appendicectomy	OR 0.54 95% CI 0.37 to 0.78 P = 0.001	●○○	antibiotics
[13] Systematic review	Mainly adults, mean age 28.2 years (range 13–75 years), suspected acute appendicitis based on disease history, clinical status, and laboratory findings 5 RCTs in this analysis	**Mean cure (within 2 weeks [free of symptoms such as abdominal pain, fever, inflammatory parameters] and without major complication [including recurrence] within 1 year)** 97% with appendicectomy 73% with antibiotics Absolute numbers not reported 486 people in analysis of appendicectomy; 415 people in analysis of antibiotics	The review pooled data for each group and calculated 95% CI Appendicectomy: 97% (95% CI 94% to 99%) Antibiotics: 73% (95% CI 63% to 82%) Mean cure rates were higher with appendicectomy, but the review did not report a between-group P value		
[13] Systematic review	Mainly adults, mean age 28.2 years (range 13–75 years), suspected acute appendicitis based on disease history, clinical status, and laboratory findings 5 RCTs in this analysis	**No major complications (including the need for further [invasive] treatment or prolonged admission [e.g., abscesses, ileus, deep wound infection, recurrence, re-operation, secondary perforation])** 97% with appendicectomy 83% with antibiotics Absolute numbers not reported 486 people in analysis of appendicectomy; 415 people in analysis of antibiotics	The review pooled data for each group and calculated 95% CI Appendicectomy: 97% (95% CI 93% to 99%) Antibiotics: 83% (95% CI 72% to 91%) Proportion of people with no major complications was higher with appendicectomy, but the review did not report a between-group P value		
[13] Systematic review	Mainly adults, mean age 28.2 years (range 13–75 years), suspected acute appendicitis based on disease history, clinical status, and laboratory findings 5 RCTs in this analysis	**No minor complications (e.g., superficial wound infections, negative appendix at histology [no appendicitis], diarrhoea, urinary tract infection)** 91% with appendicectomy 96% with antibiotics Absolute numbers not reported 486 people in analysis of appendicectomy; 415 people in analysis of antibiotics	The review pooled data for each group and calculated 95% CI Appendicectomy: 91% (95% CI 83% to 96%) Antibiotics: 96% (95% CI 93% to 97%) Proportion of people with no minor complications was higher with antibiotics, but the review did not report a between-group P value		
[14] Systematic review	Adults with a diagnosis of uncomplicated acute appendicitis Analysis included 4 RCTs with well-defined diagnostic	**Complications (antibiotics: perforated or gangrenous appendix, peritonitis, or wound infection [in people who failed antibiotics and had appendicectomy subsequently]; appendicectomy: perforated appendicitis, peritonitis, or wound infection)**	RR 0.69 95% CI 0.54 to 0.89 P = 0.004	●○○	antibiotics

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	or treatment protocols	84/470 (18%) with antibiotics 108/430 (25%) with appendicectomy			
[14] Systematic review	Adults with a diagnosis of uncomplicated acute appendicitis Analysis included 4 RCTs with well-defined diagnostic or treatment protocols	**Risk of complicated appendicitis** 54/470 (11%) with antibiotics 131/430 (31%) with appendicectomy Full definition of what was included or excluded under this outcome not reported	RR 0.46 95% CI 0.19 to 1.12 P = 0.09 Significant heterogeneity: I^2 = 82%, P <0.001 A sensitivity analysis removing 1 RCT with high crossover found a similar result, but there was still significant heterogeneity among groups (RR 0.58, 95% CI 0.18 to 1.90; I^2 = 74%)	⟷	Not significant

Mortality (from appendicitis)

Surgery compared with antibiotics We don't know whether appendicectomy and antibiotics differ in effectiveness at reducing mortality from appendicitis in adults with uncomplicated acute appendicitis (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[15] Systematic review	Adults with acute uncomplicated appendicitis (no abscess or phlegmon) 5 RCTs in this analysis	**Mortality** with antibiotics with appendicectomy Review stated that no deaths were reported in any of the studies			

No data from the following reference on this outcome. [13] [14]

Length of hospital stay

Surgery compared with antibiotics We don't know whether appendicectomy and antibiotics differ in effectiveness at reducing length of hospital stay in adults with uncomplicated acute appendicitis (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Length of hospital stay					
[13] Systematic review	Mainly adults, mean age 28.2 years (range 13–75 years), suspected acute appendicitis based on disease history, clinical status, and laboratory findings 4 RCTs in this analysis	**Duration of hospital stay , days** with antibiotics with appendicectomy 821 people in this analysis	Mean difference 0.66 days 95% CI 0.44 days to 0.87 days P <0.0001 1 RCT in the review was not included in the analysis; the review reported this was based on visual inspection, but did not report any further reason for its exclusion	○○○	appendicectomy
[14] Systematic review	Adults with a diagnosis of uncomplicated acute appendicitis Analysis included 4 RCTs with well defined-diagnostic	**Length of primary hospital stay, days (antibiotics: days of admission for people treated with antibiotics and discharged with antibiotics; appendicectomy: days of admission for people treated with appendicec-**	Mean difference +0.20 days 95% CI –0.16 days to +0.87 days P = 0.29	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	or treatment protocols	**tomy and discharged with further follow-up)** with antibiotics with appendicectomy 900 people in this analysis			
[15] Systematic review	Adults with acute uncomplicated appendicitis (no abscess or phlegmon) 5 RCTs in this analysis	**Length of hospital stay , days** with antibiotics with appendicectomy 980 people in this analysis	Mean difference +0.34 days 95% CI –0.06 days to +0.73 days P = 0.09	⟷	Not significant

Return to normal activities

Surgery compared with antibiotics Antibiotics may be more effective than appendicectomy at reducing the duration of sick leave or disability in adults with uncomplicated acute appendicitis. However, results vary based on the analysis performed (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Sick leave days					
[13] Systematic review	Mainly adults, mean age 28.2 years (range 13–75 years), suspected acute appendicitis based on disease history, clinical status, and laboratory findings 2 RCTs in this analysis	**Duration of sick leave , days** with antibiotics with appendicectomy 491 people in this analysis	Mean difference –0.69 days 95% CI –1.65 days to +0.27 days	⟷	Not significant
[15] Systematic review	Adults with acute uncomplicated appendicitis (no abscess or phlegmon) 3 RCTs in this analysis	**Duration of sick leave or disability** with antibiotics with appendicectomy 860 people in this analysis	Standard mean difference –0.19 95% CI –0.06 to –0.33 P = 0.005	○○○	antibiotics

No data from the following reference on this outcome. [14]

Quality of life

No data from the following reference on this outcome. [13] [14] [15]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[13] Systematic review	Mainly adults, mean age 28.2 years (range 13–75 years), suspected acute appendicitis based on disease history, clinical status, and laboratory findings	**Adverse effects** with antibiotics with appendicectomy The review reported on major and minor complications (see 'treatment success' outcome). However, it did not report individual adverse effects separately			
[14] Systematic review	Adults with a diagnosis of uncomplicated acute appendicitis Analysis included 4 RCTs with well-defined diagnostic or treatment protocols	**Re-admissions with recurrence of symptoms** with antibiotics with appendicectomy The review reported that, of 345 people with initial successful treatment with antibiotics: 68 people (20%) were re-admitted with recurrence of symptoms, of which 65 had subsequent appendicectomy (9 perforated, 48 phlegmonous, 4 gangrenous, 4 normal)	Significance not reported		
[15] Systematic review	Adults with acute uncomplicated appendicitis (no abscess or phlegmon) 5 RCTs in this analysis	**Recurrence of symptoms** with antibiotics with appendicectomy The review reported that, in the 5 RCTs, recurrence rates in the antibiotic group were: 7/20 (35%), 16/128 (13%), 14/202 (7%) or 15/119 (13%; per protocol analysis), 4/40 (10%), and 30/120 (25%)			

Further information on studies

[13] [14] [15] **Comparison of the three systematic reviews:** Each of the three reviews reported different outcomes and came to slightly different conclusions. Hence, we have reported all three reviews. The reviews compared antibiotic treatment (any type given intravenously or orally) compared with surgery (including open or laparoscopic appendicectomy). The first review (5 RCTs, 901 people) included all people with suspected acute appendicitis at any age. [13] The second review (4 RCTs, 900 people) included adults with uncomplicated acute appendicitis only, with well-defined diagnostic and treatment protocols. [14] It excluded two RCTs included in the first review, citing that one RCT (80 people) had been retracted, and another RCT (290 people) had unclear randomisation. However, it included one quasi-randomised RCT (369 people) that was excluded from the first review because of weak methods (allocation by birth date, large cross-over). The quasi-randomised RCT randomised people by date of birth (odd or even date), and there was substantial cross-over between groups, with 52% of people completing antibiotics and 92% of people completing surgery, and the rest crossing over to the other intervention. The second review reported a sensitivity analysis excluding these data. The third review (5 RCTs, 980 people) included all people with suspected uncomplicated acute appendicitis at any age. [15] It included all four RCTs included in the second review, and the retracted RCT that was reported in the first review but excluded in the second review.

[13] The review reported that the overall quality of the five included RCTs were low to moderate, and the randomisation methods were not well reported. The review noted previous reports that antibiotic prophylaxis was effective in preventing postoperative complications after appendicectomy. However, only two RCTs mentioned the use of prophylactic antibiotics with surgery, one RCT did not apply prophylactic antibiotics, and for the other two RCTs it was unknown. The review reported that none of the RCTs mentioned if people with antibiotics "had an appendicectomy or were followed up in another hospital other than the research hospital", and highlighted that

this could bias the results. The review included all people with suspected acute appendicitis; therefore, people with complicated appendicitis may have been included. The age of people in the five RCTs ranged from 13 to 75 years, although four RCTs only included people aged 17 years or older. Participants in the RCTs were mainly male (73.8%).

[14] The review noted that routine radiological confirmation (ultrasonography, computed tomography [CT]) of the diagnosis was used in two RCTs, some people had scans in one further RCT, and no scans were undertaken in one RCT. The latter RCT only included men aged 18 to 50 years. The review performed a sensitivity analysis excluding one quasi-randomised RCT with large cross-over between groups. Although this affected the point estimate of results, it did not alter the significance or direction of the pooled results for the outcomes of complications, length of hospital stay, or risk of complicated appendicitis. It noted that about 1 in 5 people were likely to be re-admitted after initial successful treatment with antibiotics, and of those who were re-admitted, 1 in 5 may have had complicated appendicitis. It reported that antibiotic treatment was associated with a 63% success rate at 1 year (277/438 people with antibiotics had no further symptoms at 1 year).

[15] The review found no significant difference between groups in duration of pain (3 RCTs, 688 people, standard mean difference [SMD] –0.13, 95% CI –0.28 to + 0.03), but found significantly less utilisation of pain medication in the antibiotic group compared with the appendicectomy group (2 RCTs, 120 people, SMD –1.55, 95% CI –1.14 to –1.96). The review noted that the quality of the RCTs ranged from poor to fair, and only one study described withdrawals and dropouts. It noted that, in trials with both a surgical and a non-surgical arm, comparisons between treatment groups are inevitably associated with bias for both investigators and participants. The review noted that optimal antibiotic therapy was not compared with optimal surgical therapy in any of the studies. The antibiotic combination used in two RCTs had high levels of resistance in Europe, while the surgical technique used influences morbidity. It reported that none of the studies standardised the technique, and that laparoscopic appendicectomy, which has been associated with fewer postoperative complications, was the least preferred technique in four studies. Lastly, it noted that the studies included a high proportion of perforated or gangrenous appendix (ranging from 5% for perforated to 48% for gangrenous).

Comment:

It is complicated and difficult to compare two different treatment modalities in which benefits and harms may only occur in one group (for example, postoperative complications and removal of normal appendix with surgery, and recurrence with antibiotics).

The first review concluded that "appendectomy remains the standard treatment for acute appendicitis. Antibiotic treatment might be used as an alternative treatment in a good quality RCT, or in certain populations or conditions where surgery is contraindicated". [13] The second review concluded that "antibiotics are both effective and safe as primary treatment for people with uncomplicated acute appendicitis. Initial antibiotic treatment merits consideration as a primary treatment option for early uncomplicated appendicitis". [14] The third review concluded that "non-operative management of uncomplicated appendicitis was associated with significantly fewer complications, better pain control, and shorter sick leave, but overall had inferior efficacy because of the high rate of recurrence in comparison with appendectomy". [15]

We found one further systematic review (search date 2012, 5 RCTs, 983 people). [18] However, it included one RCT (32 people) on late-presenting appendicitis that was not included in the other three reviews, and omitted one large RCT (243 people) [19] that was included in the other three reviews. The reason for exclusion was not stated. The review found no significant difference between groups in length of hospital stay (5 RCTs, 983 people; weighted mean difference [WMD] +0.01, 95% CI –0.01 to +0.03; significant heterogeneity, I^2 = 99.9%, P <0.00001) or complications (4 RCTs, 693 people; OR 0.86, 95% CI 0.59 to 1.26). It found a significantly shorter time to work with antibiotics (2 RCTs, 284 people; WMD –5.20, 95% CI –6.99 to –3.40, P <0.00001) but there was significant heterogeneity in this result (I^2 = 98.6%, P <0.00001).

Comments on the clinical applicability of the evidence:
The use of antibiotics to treat appendiceal abscess is well established, [8] but their use in managing uncomplicated acute appendicitis is unclear.

Many of the RCTs evaluated in the three systematic reviews were poorly designed, with methodological flaws and bias, thus limiting their applicability to clinical practice. Some of the shortcomings from the RCTs have arisen from their study protocol. For example, the diagnosis of uncomplicated appendicitis was confirmed by routine CT in only one RCT. [19] The RCTs also used different antibiotics with different modes of delivery and different length of treatment. Ineffective antibiotic treatment of appendicitis from a short course or community resistance could lead to increased rates of initial treatment failure. Weaknesses in the study design of the RCTs have also led to potential bias against surgery. For example, the short 1-year follow-up used in the RCTs is problem-

atic. Recurrence following antibiotic treatment may be underestimated, as appendicitis may recur beyond 1 year. Furthermore, the RCTs did not discuss postoperative details of surgery for recurrent appendicitis. A second episode of appendicitis may lead to surgery, which may be more difficult to perform and lead to more complications. The majority of complications from surgery were reported from one RCT, [20] but this study did not separate out the complications based on the type of appendicectomy technique used (open or laparoscopic). In fact, surgical technique was not reported or analysed in the RCTs. If open appendicectomy was the predominant procedure used in the RCTs, this could lead to bias against surgery as laparoscopic appendicectomy has been shown to provide decreased rates of wound infection, less pain, and a quicker return to work compared with open appendicectomy. [16] Furthermore, the use of prophylactic antibiotics with surgery can lower the rates of postoperative infectious complications, [21] but this was only reported in two RCTs.

Despite the methodological flaws and bias of the studies, useful information can still be gleaned from their findings. The evidence suggests that treating a first episode of uncomplicated appendicitis with antibiotics may be successful in reducing complications compared with surgery. Antibiotics may also reduce analgesia requirements, and duration of sick leave and disability, when compared with surgery. Clinicians should be aware of these results when consenting people to treatment for appendicitis. People with appendicitis should not be treated with antibiotics without stressing the possibility of recurrence or treatment failure during the first or subsequent admission, requiring surgery. If antibiotics are considered for the primary management of uncomplicated acute appendicitis, this diagnosis must first be confirmed by CT scan to assist in excluding complicated appendicitis and/or other diagnoses, such as cancer. [22]

Clinical guide:
Until better-quality evidence is available from further trials, the current evidence does not support a change of practice to medical management of uncomplicated appendicitis. Ongoing trials comparing antibiotic treatment versus appendicectomy are being carried out in Finland (APPAC), Italy (ASAA), Holland (APAC), and the US (Appy-PAT). [23]

GLOSSARY

Negative appendix at histology Term used to describe an appendix that has been surgically removed as a result of suspected appendicitis, but is then found to be normal on histological evaluation.

Phlegmon Inflammatory, soft tissue mass (often palpable) enclosing an inflamed appendix with no drainable pus.

Uncomplicated appendicitis Inflamed appendix without necrosis, gangrene, perforation, or abscess, and with no peritoneal contamination.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Surgery versus antibiotics Four systematic reviews added. [13] [14] [15] [18] Categorisation changed from 'trade-off between benefits and harms' to 'likely to be beneficial'.

REFERENCES

1. Addiss DG, Shaffer N, Fowler BS, et al. The epidemiology of appendicitis and appendectomy in the United States. *Am J Epidemiol* 1990;132:910–925.[PubMed]
2. Buckius MT, McGrath B, Monk J, et al. Changing epidemiology of acute appendicitis in the United States: study period 1993–2008. *J Surg Res* 2012;175:185–190.[PubMed]
3. Centers for Disease Control and Prevention. Number, rate, and standard error of all-listed surgical and nonsurgical procedures for discharges from short-stay hospitals, by selected procedure categories: United States, 2007. Available online at http://www.cdc.gov/nchs/data/nhds/4procedures/2007pro4_numberrate.pdf (last accessed 16 October 2014).
4. Health and Social Care Information Centre (UK). Hospital episode statistics, admitted patient care – England 2006–2012: main operations summaries. Available online at http://www.hscic.gov.uk/searchcatalogue?q=title%3A%22Hospital+Episode+Statistics%2C+Admitted+patient+care+-+England%22&area=&size=10&sort=Relevance (last accessed 16 October 2014).
5. National Surgical Research Collaborative. Multicentre observational study of performance variation in provision and outcome of emergency appendicectomy. *Br J Surg* 2013;100:1240–1252.[PubMed]
6. Ingraham AM, Cohen ME, Bilimoria KY, et al. Comparison of outcomes after laparoscopic versus open appendectomy for acute appendicitis at 222 ACS NSQIP hospitals. *Surgery* 2010;148:625–637.[PubMed]
7. Livingston EH, Woodward WA, Sarosi GA, et al. Disconnect between incidence of nonperforated and perforated appendicitis: implications for pathophysiology and management. *Ann Surg* 2007;245:886–892.[PubMed]
8. Andersson RE. The natural history and traditional management of appendicitis revisited: spontaneous resolution and predominance of prehospital perforations imply that a correct diagnosis is more important than an early diagnosis. *World J Surg* 2007;31:86–92.[PubMed]
9. Carr NJ. The pathology of acute appendicitis *Ann Diagn Pathol* 2000;14:46–58.[PubMed]
10. Liu K, Fogg L. Use of antibiotics alone for treatment of uncomplicated acute appendicitis: a systematic review and meta-analysis. *Surgery* 2011;150:673–683.[PubMed]
11. Cobben LP, de Van Otterloo AM, Puylaert JB. Spontaneously resolving appendicitis: frequency and natural history in 60 patients. *Radiology* 2000;215:349–352.[PubMed]
12. Kirshenbaum M, Mishra V, Kuo D, et al. Resolving appendicitis: role of CT. *Abdom Imaging* 2003;28:276–279.[PubMed]
13. Wilms IM, de Hoog DE, de Visser DC, et al. Appendectomy versus antibiotic treatment for acute appendicitis. In: The Cochrane Library, Issue 4, 2014. Chichester, UK: John Wiley & Sons, Ltd. Search date 2011.[PubMed]
14. Varadhan KK, Neal KR, Lobo DN. Safety and efficacy of antibiotics compared with appendicectomy for treatment of uncomplicated acute appendicitis: meta-analysis of randomised controlled trials. *BMJ* 2012;344:e2156.[PubMed]
15. Mason RJ, Moazzez A, Sohn H, et al. Meta-analysis of randomized trials comparing antibiotic therapy with appendectomy for acute uncomplicated (no abscess or phlegmon) appendicitis. *Surg Infect (Larchmt)* 2012;13:74–84.[PubMed]
16. Sauerland S, Jaschinski T, Neugebauer EA. Laparoscopic versus open surgery for suspected appendicitis. In: The Cochrane Library, Issue 4, 2014. Chichester, UK: John Wiley & Sons, Ltd. Search date 2010.[PubMed]
17. Andersson R, Lambe M, Bergstrom R. Fertility patterns after appendicectomy: historical cohort study. *BMJ* 1999;318:963–967.[PubMed]
18. Liu ZH, Li C, Zhang XW, et al. Meta-analysis of the therapeutic effects of antibiotic versus appendicectomy for the treatment of acute appendicitis. *Exp Ther Med* 2014;7:1181–1186.[PubMed]

19. Vons C, Barry C, Maitre S, et al. Amoxicillin plus clavulanic acid versus appendicectomy for treatment of acute uncomplicated appendicitis: an open-label, non-inferiority, randomised controlled trial. *Lancet* 2011;377:1573–1579.[PubMed]
20. Hansson J, Körner U, Khorram-Manesh A, et al. Randomized clinical trial of antibiotic therapy versus appendicectomy as primary treatment of acute appendicitis in unselected patients. *Br J Surg* 2009;96:473–481.[PubMed]
21. Andersen BR, Kallehave FL, Andersen HK. Antibiotics versus placebo for prevention of postoperative infection after appendectomy. In: The Cochrane Library, Issue 4, 2014. Chichester, UK: John Wiley & Sons, Ltd. Search date 2005.[PubMed]
22. Andersson RE, Petzold MG. Nonsurgical treatment of appendiceal abscess or phlegmon: a systematic review and meta-analysis. *Ann Surg* 2007;246:741–748.[PubMed]
23. National Institutes of Health (US). ClinicalTrials.gov. Available online at: http://clinicaltrials.gov/ (last accessed 16 October 2014).

Nigel D'Souza
Specialist Registrar in General Surgery
Wessex Deanery
UK

Karen Nugent
Senior lecturer
University Surgical Unit
Southampton General Hospital
Southampton
UK

Competing interests: NDS and KN declare that they have no competing interests.
NDS and KN would like to acknowledge the previous contributors of this review, including David Humes, William Speake, and John Simpson.

Disclaimer

GRADE **Evaluation of interventions for Appendicitis.**

Important outcomes	Length of hospital stay, Mortality (from appendicitis), Quality of life, Return to normal activities, Treatment success								
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of surgery compared with antibiotics for acute appendicitis?									
at least 4 (at least 900) [13] [14] [15]	Treatment success	Surgery versus antibiotics	4	–3	–1	–2	0	Very low	Quality points deducted for weak methods (unclear allocation concealment, blinding, and randomisation), uncertainty of diagnosis, and incomplete reporting of results; consistency point deducted for significant heterogeneity and different outcome measures; directness points deducted for unclear clinical generalisability (unclear if antibiotics used with surgery, no comparison of optimal therapies, no outcomes beyond 1 year, predominantly males, adults only)
5 (at least 900) [15]	Mortality (from appendicitis)	Surgery versus antibiotics	4	–3	0	–2	0	Very low	Quality points deducted for weak methods (unclear allocation concealment, blinding, and randomisation), uncertainty of diagnosis, and incomplete reporting of results; directness points deducted for unclear clinical generalisability (unclear if antibiotics used with surgery, no comparison of optimal therapies, no outcomes beyond 1 year, predominantly males, adults only)
at least 4 (at least 821) [13] [14] [15]	Length of hospital stay	Surgery versus antibiotics	4	–3	0	–2	0	Very low	Quality points deducted for weak methods (unclear allocation concealment, blinding, and randomisation), and uncertainty of diagnosis; directness points deducted for unclear exclusion of trial, and unclear clinical generalisability (unclear if antibiotics used with surgery, no comparison of optimal therapies, no outcomes beyond 1 year, predominantly males, adults only)
at least 3 (at least 491) [13] [15]	Return to normal activities	Surgery versus antibiotics	4	–3	0	–2	0	Very low	Quality points deducted for weak methods (unclear allocation concealment, blinding, and randomisation) and uncertainty of diagnosis; directness points deducted for unclear clinical generalisability (unclear if antibiotics used with surgery, no comparison of optimal therapies, no outcomes beyond 1 year, predominantly males, adults only)

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.